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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,954	SOLOMON ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,27-39 and 122-141* is/are pending in the application.

4a) Of the above claim(s) *1-13,29 and 132-141* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27, 28, 30-39 and 122-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-13,27-39 and 122-141* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group IV (claims 27-39), late onset Alzheimer's disease, and beta-amyloid (Aβ) in the Response and Amendment filed 11 March 2004 is acknowledged. Applicant's request to rejoin early onset Alzheimer's disease, late onset Alzheimer's disease, and presymptomatic Alzheimer's disease is hereby *granted.* The other diseases remain withdrawn from consideration. The traversal is on the ground(s) that **(a)** the composition of the claims of Group IV has been amended to specific that the pharmaceutical composition is in unit dosage form, and **(b)** claims 1-13 have been amended to depend from elected claim 27. This is not found persuasive because the restriction requirement as set forth in the previous Office Action (11 September 2003) was a proper showing of lack of unity for the claims as originally presented. Amending the claims after the establishment of lack of unity can not void the restriction requirement. The Examiner notes however that the restriction now is clearly between 2 sets of product and 2 sets of method claims. If the product claims (claims 27-39 and 122-131) are subsequently found allowable, withdrawn method claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Method claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

2. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined method claims will be withdrawn, and the rejoined method claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and method claims may be maintained. Withdrawn method claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the method claims should be amended during prosecution either to maintain dependency on the method claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

3. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the Examiner before the patent issues. See MPEP § 804.01.

4. Claims **1-13** and **132-141** are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Response and Amendment filed 11 March 2004.

5. Claim **29** is directed to inventions that are independent or distinct from the invention elected (claims 27, 28, 30-29) for the following reasons: claim 29 is drawn to diseases not

included in the elected invention. Each disease listed in claim 29 requires separate and distinct field of search and consideration. Since applicant has elected Alzheimer's disease, this claim is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

6. The restriction requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, and/or Claims

7. The Preliminary Amendment filed 3 May 2001 has been received and entered in full.

8. The Preliminary Amendment filed 7 August 2001 has been received and entered in full.

9. The Preliminary Amendment filed 12 August 2002 has been received and entered in full.

10. The Application Data Sheet filed 11 March 2004 has been received and entered in full.

Specification

11. The disclosure is objected to because of the following informalities: misspelling "polyepeptide" (pp. 9 line 20); mixed type "ons*et Alzhei*mer's" (pp. 9 line 32); misspelling "deuced" (pp. 14 line 18); spaces "Schenk *et al.* ," (pp. 27 line 8); inconsistent abbreviation "βA" (pp. 27 line 26); citations mixed, incoherent (pp. 27 lines 27-29); double closed parentheses "1997))" (pp. 71 line 4). Appropriate correction is required.

Sequence Rules

12. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein. This application discloses an amino acid sequence in Figure 25. In addition, the epitope "EFRH" (listed as SEQ ID NO: 1) must be accompanied by its SEQ ID NO throughout the Specification. Appropriate correction is required.

Drawings

13. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: Figure 1 refers to "Lanes" which are not present in the drawing. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

14. The drawings are objected to because Figures 14, 15, and 17 are too dark to decipher any information contained therein. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

15. Claims **28, 30,** and **31** are objected to because of the following informalities: said claims recite non-elected subject matter. The non-elected subject matter therein has not been examined on its merits. Appropriate correction is required.

Obvious-Type Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims **27, 28, 30-39,** and **122-131** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-11** of U.S. Patent No. 6,703,015 B1 (9 March 2004) Solomon & Frenkel.

17. Although the conflicting claims are not identical, they are not patentably distinct from each other because US 6,703,015 claims a pharmaceutical composition in unit dosage form, comprising a pharmaceutically acceptable carrier and, as an active ingredient, a filamentous bacteriophage displaying an epitope of β-amyloid which elicit Aβ binding antibodies against said epitopes when administered to a subject, wherein said antibodies inhibit aggregation of said β-amyloid in the subject and/or cause disaggregation of β-amyloid aggregates in said subject. The invention of US 6,703,015 is encompassed by the invention of claims 27-39 in the instant Application which is a pharmaceutical composition in unit dosage form, comprising a pharmaceutically acceptable carrier and, as an active ingredient, a display vehicle displaying a polypeptide, said polypeptide representing at least on epitope of an aggregating protein such as

β-amyloid which elicit antibodies against said epitope when administered to a subject, wherein said antibodies inhibit aggregation in the subject and/or cause disaggregation of aggregates in said subject. Therefore the invention of the instant application as in claims 27-39 is not patentably distinct from the invention of US 6,703,015.

18. Furthermore the invention of US 6,703,015 is commensurate with the invention of claims 122-131 in the instant Application which is a pharmaceutical composition in unit dosage form, comprising a pharmaceutically acceptable carrier and, as an active ingredient, a virus displaying a polypeptide, said polypeptide comprising at least on epitope of β-amyloid such as β-amyloid which elicit antibodies against said epitope when administered to a subject, wherein said antibodies inhibit aggregation in the subject and/or cause disaggregation of aggregates in said subject. Therefore the invention of the instant application as in claims 122-131 is not patentably distinct from the invention of US 6,703,015.

19. Claims **27, 28, 30-39,** and **122-131** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **15** and **16** of copending Application No. 09/808,037 {herein cited as US Patent Application Publication No. US 2002/0052311 A1 (2 May 2002) Solomon & Frenkel}.

20. Although the conflicting claims are not identical, they are not patentably distinct from each other because '037 claims a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a viral display vehicle displaying a therapeutic molecule. A reasonably broad reading of the claims of '037 include the invention of the instant application of claims 27-39 in the instant Application which is a pharmaceutical composition in

unit dosage form, comprising a pharmaceutically acceptable carrier and, as an active ingredient, a display vehicle displaying a polypeptide, said polypeptide representing at least on epitope of an aggregating protein such as β-amyloid which elicit antibodies against said epitope when administered to a subject, wherein said antibodies inhibit aggregation in the subject and/or cause disaggregation of aggregates in said subject. Therefore the invention of the instant application as in claims 27-39 is not patentably distinct from the invention of '037.

21. Furthermore the invention of '037 encompasses the invention of claims 122-131 in the instant Application which is a pharmaceutical composition in unit dosage form, comprising a pharmaceutically acceptable carrier and, as an active ingredient, a virus displaying a polypeptide, said polypeptide comprising at least on epitope of β-amyloid such as β-amyloid which elicit antibodies against said epitope when administered to a subject, wherein said antibodies inhibit aggregation in the subject and/or cause disaggregation of aggregates in said subject. Therefore the invention of the instant application as in claims 122-131 is not patentably distinct from the invention of '037.

22. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. Claims **27, 28, 30-39,** and **122-131** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **15, 16,** and **39** of copending Application No. 10/384788 {herein cited as US Patent Application Publication No. US 2004/0013647 A1 (22 January 2004) Solomon & Frenkel}.

24. Although the conflicting claims are not identical, they are not patentably distinct from each other because '788 claims a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a viral display vehicle displaying a therapeutic molecule. A reasonably broad reading of the claims of '788 include the invention of the instant application of claims 27-39 in the instant Application which is a pharmaceutical composition in unit dosage form, comprising a pharmaceutically acceptable carrier and, as an active ingredient, a display vehicle displaying a polypeptide, said polypeptide representing at least on epitope of an aggregating protein such as β-amyloid which elicit antibodies against said epitope when administered to a subject, wherein said antibodies inhibit aggregation in the subject and/or cause disaggregation of aggregates in said subject. Therefore the invention of the instant application as in claims 27-39 is not patentably distinct from the invention of '788.

25. Furthermore the invention of '788 encompasses the invention of claims 122-131 in the instant Application which is a pharmaceutical composition in unit dosage form, comprising a pharmaceutically acceptable carrier and, as an active ingredient, a virus displaying a polypeptide, said polypeptide comprising at least on epitope of β-amyloid such as β-amyloid which elicit antibodies against said epitope when administered to a subject, wherein said antibodies inhibit aggregation in the subject and/or cause disaggregation of aggregates in said subject. Therefore the invention of the instant application as in claims 122-131 is not patentably distinct from the invention of '788.

26. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

27. Claims **27, 28, 30-39,** and **122-131** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *a pharmaceutical composition in unit dosage form, comprising a pharmaceutically acceptable carrier and, as an active ingredient, a filamentous bacteriophage displaying an epitope selected from the group consisting of EFRH, DAEFRH, DAEFRHD, DAEFRHDSG, and Aβ (β-amyloid) which elicit Aβ binding antibodies against said epitopes when administered to a subject, wherein said antibodies inhibit aggregation of said β-amyloid in the subject and/or cause disaggregation of β-amyloid aggregates in said subject,* does not reasonably provide enablement for *other display vehicles, other viruses, other epitopes, other aggregating proteins, any other plaque related disease, or prevention thereof.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

28. The claims are drawn very broadly to an endless number of possible display vehicles to with any one of the massive number of possible epitopes for the known aggregating proteins be used in a myriad of known plaque related disorders. The language of said claims specifically encompasses *in vivo* therapeutic uses.

29. The specification teaches that filamentous bacteriophages displaying an epitope selected from the group consisting of EFRH, DAEFRH, DAEFRHD, and DAEFRHDSG elicit

Aβ binding antibodies (Figure 25). Said filamentous bacteriophages slow and/or inhibit Aβ aggregation *in vitro* and bind to Aβ deposits *in vivo* (Examples 5-14). In the Specification, Examples 1-4 show the generation of the claimed filamentous bacteriophage which binds Aβ(1-16) peptide. Example 5 shows that the claimed filamentous bacteriophage can lessen the toxicity of β-amyloid in PC12 cells *in vitro*. Example 6 examined the effect of 508(Fv) on disruption of the βAP fibril using a ThT fluorescence assay. The results displayed that 508(Fv) incubated with pre-formed βAP fibrils disrupted the fibril structure indicating extensive deterioration of fibril morphology. Example 7 displayed the ability of filamentous phage to enter the central nervous system (CNS) via olfactory track in female Balb/c mice. The example showed that phages were evident in the olfactory bulb and hippocampus after one day following single intranasal administration of 10^{11} phages and after several days phages were only detected in the olfactory bulb of one the mice and at 28 days following administration no phages were evident. Example 14 that serum extracted from said immunized mice can be used to decrease the percentage of fibrils in an *in vitro* assay. It is clear that this does not show prevention since fibrils formed in all the samples shown. It is unclear whether the serum was added before the fibril seeds have formed or after, in that the serum stopped or slowed the formation of already formed fibrils or if it disassembled already formed fibrils.

30. However, the specification as filed fails to provide any guidance for the successful manufacture or use of any other display vehicles, with any other epitopes, for any other plaque related diseases or disorders. And since resolution of the various complications in regards to targeting any given plaque (also known as aggregates and inclusions) in the myriad of known plaque related disorders using any one of the massive number of possible epitopes for the known

aggregating proteins is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to the invention as claimed *in vivo* would require the *de novo* determination of formulations with known myriad of known plaque related disorders using any one of the innumerable number of possible epitopes for the known aggregating proteins to correlate with the disaggregation and/or prevention of aggregation in any one or all of the applicable instances. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

31. Additionally, a person skilled in the art would recognize that predicting the efficacy of using any given display vehicle for the massive number of known plaque related disorders using any one of the countless number of possible epitopes for the known aggregating proteins *in vivo* based solely on its performance of a single example as highly problematic (see MPEP §2164.01). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed filamentous bacteriophages displaying an epitope selected from the group consisting of EFRH, DAEFRH, DAEFRHD, and DAEFRHDSG in *in vivo*, such a disclosure would not be considered enabling since the state of plaque related diseases is highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;

(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

32. The following references are cited herein to illustrate the state of the art of Alzheimer's disease and active immunization.

33. On the nature of the invention, specially the astronomical number of possible epitopes from any one or all of the hundreds of known aggregating proteins, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly

small peptides, conjugation appears to be required for promoting an effective immune response. As Goldsby *et al.* (2002) Kuby Immunology Chapter 18 "Vaccines" (pp. 449-465) teaches that active immunization is not predictable as peptides are not generally immunogenic.

34. Furthermore Su *et al.* (6 February 1999) "Intravascular infusions of soluble β-amyloid compromise the blood-brain barrier, activate CNS glial cells and induce peripheral hemorrhage." Brain Research **818**(1): 105-117 teaches that rats receiving twice daily intravascular administrations of $A\beta_{1-40}$ suffered damage to their blood-brain-barrier and elevated inflammation responses in their brains evidenced by activated microglia (Figures 2-4; pp. 113). Thus absent concrete guidance on how to practice the instant invention involving administration of an immunogenic peptide comprising at least one unnatural amino acid the skilled artisan is confronted with an undue burden of experimentation. First the skilled artisan must manufacture the appropriate peptide/display vehicle combination, then test each one to determine which have the desirable immunological effect. Therefore the claims as currently presented constitute an invitation to experiment and since it is held that "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure." {see *Genetech INC. v. Novo Nordisk A/S* [42 USPQ2d 1001, 1005] (CAFC 1997)}.

35. Regarding the breadth of the claims, Goldfarb and Brown (1995) "The Transmissible Spongiform Encephalopathies." Annu. Rev. Med. **46**: 57-66 teaches that prion disease also known as transmissible spongiform encephalopathies (TSEs) encompasses kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and fatal familial insomnia (Abstract). All of these diseases share a common element of an aggregating protein (prion

protein) however the diseases are caused by different mutations and various isoforms may or may not be infectious (Table 1 and Table 2). In addition, Kovács *et al.* (2002) "Mutations of the Prion Protein Gene." J. Neurol. **249**: 1567-1582 teaches that different mutations of the prion protein gene are responsible for different diseases with differing ages of onset and severity (Tables 1 and 2; Figures 4 and 5). Thus the skilled artisan is confronted with an undue burden of experimentation and unpredictability on how each individual isoform and/or mutation will affect the immune system of a patient. See also Elan Press Releases (18 January 2002 and 1 March 2002). It is also noted that although no deleterious effects were observed, this too could be dependent upon genetic factors of the animal receiving the immunization. Thus uncertainty is found by use of Aβ, a single example of an aggregating protein, as an immungen in regards to possible autoimmune reactions, general deleterious side effects, and variability in the production of anti-Aβ antibodies.

36. On the nature of the invention in regards to the ancillary effects of the introduction of an immune response in a mammalian nervous system, the specification must establish that the antigens injection into the subjects produce a specific immune response and do not act as pyrogens (leading to cranial swelling for example). Goldsby *et al.* (2002) Kuby Immunology 4th Ed. Chapter 18 "Vaccines" (pp. 449-465) teaches that a large quantity of experimentation necessary to evaluate all the effects of the difficulty of predicating an immune response in the nervous system. This is due to the fact that the stimulation of an immune response by an antigenic peptide does not mean that the patient has acquired protective immunity, in the case of the instant invention, the prevention of the development of an amyloid-related disease. An additional factor in "prevention" and active immunization is the successful development of

immunological memory, not always a guarantee, requiring additional experimentation. Goldsby *et al.* also teaches that peptides are not as immunogenic as proteins and it is difficult for them to elicit both humoral and cellular immunity (pp. 461).

37. Moreover on the nature of an immune response required to fulfill the goal of the preamble, Singh (1997) "Neuroautoimmunity: Pathologic Implications for Alzheimer's Disease." Gerontology **43**:79-94 teaches that inflammation may play a key role in the Alzheimer's disease pathology (pp. 86). However, the Specification does not present sufficient direction/guidance about collateral damage due to a vigorous immune response in an immunological privileged area (such as the nervous system). The Specification as filed has only demonstrated a single successful antigenic presentation of a single example (filamentous bacteriophage with Aβ epitopes) does not account for the unpredictability of the effects of aggregating protein epitopes (antigens) on the mammalian nervous system, and the breadth of the claims which fail to recite limitations for what constitutes a successful, controlled immune response in the mammalian brain, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

38. On the quantity of experimentation needed to make or use the invention based on the content of the disclosure, Castillo *et al.* (1995) "Amylin/Islet Amyloid Polypeptide: Biochemistry, Physiology, Patho-Physiology." Diabete et Metbolisme **21**: 3-25 teaches that amylin, the causative agent in islet amyloid formation in diabetes, is a 37 residue protein with a variety of actions in humans. The instant claims read on modifying/replacing one to all of the 37 positions in the amylin protein with one or any amino acid. Then injecting said modified proteins into patients to determine which, if any, have the desired effect of inducing a humoral (antibody-

based) immune response as a therapy for islet amyloidosis. This constitutes an invitation to experiment with potentially $2.08x10^{53}$ potential "immunogenic peptides" derived from a single amyloid protein (when only counting full-length wild-type and derivative amylin proteins).

39. Moreover on the quantity of experimentation required to make or use the invention based on the content of the disclosure, Tobin & Signer (December 2000) "Huntington's disease: the challenge for cell biologists." Trends in Cell Biology **10**(12): 531-536 teach that aggregates are the hallmark of polyglutamine diseases, disorders in which the causative agent is a mutant protein with an expanded stretch of glutamine residues. The polyglutamine diseases (with their corresponding protein) include Huntington's disease (Huntingtin), Spinocerebellar ataxia-1 (SCA-1), Spinocerebellar ataxia-2 (SCA-2), Spinocerebellar ataxia-3 (SCA-3), Spinocerebellar ataxia-6 (SCA-6), Spinocerebellar ataxia-7 (SCA-7), and dentatorubral pallidoluysian atrophy (DPRLA) (Table 1). To achieve the full scope of the claims as instantly presented, the skilled artisan is confronted with a Herculean task of identifying all of the applicable epitopes for all 8 polyglutamine proteins, screening and characterizing said epitopes, and then determining which, if any, meet the requirements of the claims. The Examiner notes that polyglutamine diseases are only a single group of the hundreds of known aggregating proteins such is the scope of the claims as instantly presented.

40. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the use *in vivo* of any given display vehicle with any given epitope of any given aggregation protein for the prevention or disaggregation of any and all plaques and their respective diseases as exemplified in the references herein.

41. Claims **27, 28, 30-39,** and **122-131** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

42. The claims require "display vehicle" while the claims do not require that the display vehicle to possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of display vehicles that is defined by intended function. This implies that the display vehicle is not known or must be confirmed. Withal the art recognizes that "display vehicle" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, viruses, biologically derived substances as well as proteinaceous substances, known, and unknown compounds.

43. The claims require "epitope" while the claims do not require that the epitope to possess any particular conserved structure, or other distinguishing feature, such as sequence. Thus, the claims are drawn to a genus of epitopes that is defined by originating from any one or all of any number of aggregating proteins. This implies that the epitope is not known or must be confirmed.

44. The claims require "aggregating protein" while the claims do not require that the aggregating protein to possess any particular conserved structure, or other distinguishing feature, other than aggregating. The Examiner notes that almost any protein may aggregate under the

right conditions. For instance, egg albumin will aggregate when heated to 100°C for a sufficient time. Thus, the claims are drawn to a genus of epitopes that is defined by originating from any one or all of any number of aggregating proteins. This implies that the aggregating protein is not known or must be confirmed.

45. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of desired product comprising any given display vehicle which displays any given epitope of any given aggregating protein. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

46. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the

description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

47. In the instant case, the Applicant has delineated a desired product but has not evidenced material possession of said product. This most clearly parallels the fact pattern of *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co. et al.* CAFC [(03-1304) 13 February 2004]. In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since the patent described the compound's desired function of reducing activity of the enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment

to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

48. Furthermore as pertains to the non-disclosure of an epitope, parallels the fact pattern of *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 20 January 2004) the CAFC held that "Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.

49. Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another

unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application.

50. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen."

51. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

Summary

52. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

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Elizabeth C. Kemmerer

CJN
May 6, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER